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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/595,072	05/09/2006	Frank Luyten	50304/010002	2155

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EXAMINER	
BUNNER, BRIDGET E	

ART UNIT	PAPER NUMBER
1647	

NOTIFICATION DATE	DELIVERY MODE
02/12/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

Office Action Summary	Application No.	Applicant(s)	
	10/595,072	LUYTEN ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-38* is/are pending in the application.

4a) Of the above claim(s) *30-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *24-38* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 January 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/30/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I, claims 24-29, directed to a method for the promotion of cartilage comprising administering CXCL6, in the reply filed on 17 December 2007 is acknowledged.

Claims 30-38 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 17 December 2007.

Claims 24-29 are under consideration in the instant application.

Claim Objections

1. Claims 24, 27, 28 are objected to because of the following informalities:

2. Claims 24, 27, and 28 use the acronym "CXCL6" without first defining what it represents in the independent claims. While the claims can reference acronyms, the material presented by the acronym must be clearly set forth at the first use of the acronym.

3. Claim 24, line 2 is missing a word(s) after the phrase "CXCL6 to". (Please note that this issue could be overcome by amending the claim to recite, for example, "...of CXCL6 to an individual...".)

Appropriate correction is required.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 24-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

5. Claims 24-29 are indefinite because the elements recited in the claim do not constitute proper Markush groups. The claims are indefinite in the alternative use of "and/or" because it is not clear what controls which of these limitations (see for example, claim 24). See MPEP § 2173.05(h).

6. Claims 24-29 are indefinite because the claims do not have a step that clearly relates back to the preamble. For example, there is no step indicating that cartilage or bone formation is promoted.

7. Claim 27 recites the limitation "the source of CXCL6" in line 1. There is insufficient antecedent basis for this limitation in the claim. It is noted that claim 27 depends from claim 24. However, claim 24 does not recite any sources of CXCL6.

8. Claims 24, 27-29 are indefinite because claim 24, line 1 recites "a method of treatment for the promotion of cartilage and/or bone formation". The claims are not clear because they recite both a method of treatment and a promotion of cartilage and/or bone formation.

9. Claims 25 and 26 recite the limitation "the prevention" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim. It is noted that claims 25 and 26 depend from claim 24. However, claim 24 does not recite the prevention of any disease or disorder.

10. The term "in a gradient" in claim 28 is a relative term which renders the claim indefinite. The term "in a gradient" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably

apprised of the scope of the invention. At page 19, lines 28-32, the specification discloses that a matrix allows administration of CXCL6 in a gradient to the osteochondral defect. At page 20, lines 1-3, the specification teaches matrices with a gradient in pore size and that filling such a matrix with a polymerisable solution with CXCL6 will result in a concentration gradient of CXCL6. Thus, it is not clear if the claim is referring to a matrix or a concentration gradient.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 24-29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for the promotion of hyaline cartilage and subchondral bone formation comprising administering an effective amount of CXCL6 to promote hyaline cartilage and subchondral bone formation, does not reasonably provide enablement for a method of treatment for the promotion of cartilage and/or bone formation comprising the step of administering an effective amount of CXCL6 to individual in need thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are directed to a method of treatment for the promotion of cartilage and/or bone formation comprising the step of administering an effective amount of CXCL6 to an individual in need thereof. Claim 25 recites that the method prevents or treats a cartilage or osteochondral defect. Claim 26 recites that the method prevents or treats a joint surface defect

not related to inflammation. Claim 27 recites that the source of CXCL6 is a population of CXCL6-expressing cells. Claim 28 recites that the CXCL6 is administered to a osteochondral defect in a gradient. Claim 29 recites that the method further comprises the step of administering chrondrogenic cells or precursor cells of said chondrogenic cells.

The specification of the instant application teaches that a 6x6mm osteochondral defect was made in the central part of the left medial femoral condyle in adult goats (page 24, lines 1-18). The bony defect was filled with a piece of resorbable gelatin sponge (page 24, lines 27-29). The animals in the experimental group were injected with 80-100 µl of human CXCL6 under a periostal flap sutured on the cartilage and absorbed by the gelatin sponge (page 25, lines 1-3) while the animals in the control group received nothing. Before sacrifice, the joints of the animals were evaluated for muscle atrophy, gait analysis at walk (page 25, lines 29-30). An evaluation of repair of the chondral defect was based on an optical and histological analysis of the synovial biopsy (page 25, lines 31-32; Figures 2-3). The specification teaches that in the CXCL6 treated defect, there is a repair of hyaline cartilage and underlying bone (page 26, lines 19-20). In the absence of CXCL6, the joint defect zone is vascularized and consists of fibro-cartilage (page 26, lines 17-19). The specification discloses that in the biopsy of the CXCL6-treated animals, an almost complete filling of the bone defect with newly formed subchondral bone and hyaline-like to hyaline cartilage on top was observed (page 27, lines 1-4). In the control group, the defect was filled with mixed tissue (page 27, lines 6-7).

However, the specification does not teach the promotion of all types of cartilage and bone. Relevant literature reports that there are three different types of cartilage: hyaline, elastic, and fibrocartilage, (see for example, Meyer and Wiesmann. Bone and Cartilage. 2006.

Germany: Springer (chapter 2; page 25). Hyaline cartilage is found on the articular surface of bones, the ventral aspects of ribs, in the larynx, the trachea, and in the bronchial tree. Elastic cartilage is located in the auricle of the external ear, the walls of the external auditory meatus, the Eustachian tube, the epiglottis, and parts of the larynx. Fibrocartilage is found in the annulus fibrosus of intevertebral discs, the symphysis pubis, and the junctions between large tendons and articular cartilage in large joints (Meyer and Wiesmann, page 25). It is also noted that hyaline cartilage is divided into 4 or 5 zones, depending on the differentiation of the most superficial zone into one or two compartments (Imhof et al. Invest Radiol 35(10): 581-588, 2000). At the base, the adult hyaline (articular) cartilage is bordered by the subchondral bone plate. Below the end plate zone, the subcondral bone is situated (Imhof et al., page 582, column 1; Figure 1). Imhof et al. discloses that the subchondral bone contains fatty bone marrow and trabecular bone (page 582, bottom of column 1). Regarding the instant application, though, the specification only teaches that CXCL6 administration promotes the formation of hyaline cartilage and subchondral bone. A large quantity of experimentation would be required of the skilled artisan to promote the formation of all types of cartilage and bone by the administration of CXCL6. Such experimentation is considered undue. One skilled in the art would also not be able to predict that CXCL6 would promote the formation of all cartilage and bone. The disclosure in the specification is not adequate guidance, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Additionally, as was found in Ex parte Hitzeman, 9 USPQ2d 1821 (BPAI 1987), a single embodiment may provide broad enablement in cases involving predictable factors such as mechanical or electrical elements, but more will be required in cases that involve unpredictable factors such as most chemical reactions and

physiological activity. See also In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991).

Furthermore, the specification does not teach the *prevention* of a cartilage or osteochondral defect by administration of CXCL6 in any animal. The specification does not teach the *prevention* of any joint surface defect in any animal. The term "prevent" is interpreted by the Examiner as meaning that an activity will not occur, i.e. cartilage or osteochondral defects will not occur. Undue experimentation would be required of the skilled artisan to determine the quantity of CXCL6 administered, the best route of administration, and the duration of treatment, to completely *prevent* cartilage defects, osteochondral defects, and joint surface defects.

Due to the large quantity of experimentation necessary to promote the formation of all types of cartilage and bone, as well as to prevent cartilage defects, osteochondral defects, and joint surface defects; the lack of direction/guidance presented in the specification regarding the same; the absence of working examples directed to the same; the complex nature of the invention; and the breadth of the claims, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

12. Claim 29 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 29 recites the method according to claim 24, further comprising the step of administering chondrogenic cells or precursor cells of said chondrogenic cells. The claims do not require that the chondrogenic cells or precursor cells possess any particular biological activity, nor any particular conserved structure, or other disclosed distinguishing feature. Thus, the claims are drawn to a genus of chondrogenic cells or precursor cells of said chondrogenic cells and methods of using such.

The specification of the instant application teaches that " 'chondrogenic cells' are cells capable of producing stable hyaline cartilage" (page 11, line 32 through page 12, line 1). The specification also discloses that "a precursor cell of a chondrogenic cell is a precursor cell capable of undergoing differentiation into a cell capable of producing stable hyaline cartilage" (page 12, lines 7-9).

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, there is not even identification of any particular structure or function that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. Additionally, the description of one chondrogenic cell (chondrocytes; page 15, lines 25-26) is not adequate written description of an entire genus of chondrogenic cells, precursor cells of chondrogenic cells, and all methods of using such.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed"* (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

The skilled artisan cannot envision the detailed structure and function of the encompassed chondrogenic cells and precursor cells thereof, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The polypeptide itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only specific chondrogenic cells, precursor cells of said chondrogenic cells and all methods of using such, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claim 24 is rejected under 35 U.S.C. 102(b) as being anticipated by Van Damme et al. (U.S. Patent 5,840,524; 24 November 1998).

Van Damme et al. teach the administration of granulocyte chemotactic protein 2 (GCP-2) to treat an inflammatory condition in a mammal (column 8, lines 65-67). It is well known in the art that GCP-2 is another term for CXCL6. Specifically, GCP-2 is the common ligand name while CXCL6 is the systemic name (see for example, Haringman et al., Ann Rheumatic Diseases 63(10): 1186-1194, 2004; page 1187, Table 1).

It is also noted that the recitation "for the promotion of cartilage and/or bone formation" has not been given patentable weight because the recitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951).

Conclusion

No claims are allowable.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:

Wuyts et al. Biochemistry 36(9): 2716-2723, 1997 (characterization of GCP-2)

Lindahl et al. Tissue Engineering of Cartilage and Bone. Novartis Foundation Symposium 249. 2003. UK: John Wiley and Sons, Ltd., pages 175-189 (clinical aspects of therapy with chondrocytes)

Cartilage and bone repair regeneration using post-partum derived cells:

US2005/0019865 (Kihm et al.)

US2006/0153817 (Kihm et al.)

US2006/0154366 (Brown et al.)

US2006/0154367 (Kihm et al.)

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (571) 272-0881. The examiner can normally be reached on 8:30-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

BEB
Art Unit 1647
28 January 2008

/Bridget E Bunner/
Primary Examiner, Art Unit 1647